

## **UNITED STATES AIR FORCE RESEARCH LABORATORY**

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### **THE EFFECTS OF UTRICULAR LESIONS ON SYMPATHETIC CONTROL OF CARDIOVASCULAR FUNCTION DURING +GZ STRESS**

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources – National Research Council.

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F. WESLEY BAUMGARDNER, Ph.D.  
Acting Chief, Biodynamics and Protection Division

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A handwritten signature in black ink, appearing to read "Paul Werchan". The signature is fluid and cursive, with a large initial "P" and a long, sweeping underline.

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Research Physiologist

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<b>14. ABSTRACT</b> The vestibular system has long been recognized to play an important role in autonomic control, having important influences over the gastrointestinal, cardiovascular, renal, respiratory, and oculomotor systems. The effects of vestibular stimulation and lesion have been observed in these systems. A recent theory sought to clarify the previously documented vestibular-autonomic relationships by postulating the utricles to have a predominantly sympatho-excitatory autonomic effect whereas the other vestibular end-organ systems exert a predominantly parasympatho-excitatory/sympatho-inhibitory effect. Thus this proposed research attempted to eliminate utricular sympathetic inputs by selectively destroying hair cells of the otolith organs ( of the utricles in particular) in animals by exposing them to extremely high and prolonged Gy stimulation (+, - or both). The specific measure of sympathetic function was to be changes in G- induced loss of consciousness ( G-LOC) induction time and cardiac output during +Gz stress. A utricular hair cell lesion model prolonged centrifugation of rats in the Gy axis was developed. The method of eliminating vestibular influence offers advantage of being fairly " non-invasive".					
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## THE EFFECTS OF UTRICULAR LESIONS ON SYMPATHETIC CONTROL OF CARDIOVASCULAR FUNCTION DURING +Gz STRESS

### BACKGROUND:

The vestibular system has long been recognized to play an important role in autonomic control, having important influences over the gastrointestinal, cardiovascular, renal, respiratory, and oculomotor systems. The effects of vestibular stimulation and lesions have been rather complex and ambiguous, however, as both inhibitory and excitatory effects have been observed in these systems. A recent theory sought to clarify the previously documented vestibular-autonomic relationships by postulating the utricles to have a predominantly sympatho-excitatory autonomic effect whereas the other vestibular end-organ systems exert a predominantly parasympatho-excitatory/sympatho-inhibitory effect. One straightforward method of evaluating these autonomic relationships is to monitor cardiovascular parameters such as heart rate, cardiac output and blood pressure. While the linear force and gravitational stimulation procedures have clearly demonstrated that the vestibular system plays a role in sympathetic activation, they have not differentiated the roles of the different vestibular organs in autonomic control. On the basis of neurophysiological and behavioral evidence unrelated to cardiovascular functioning per se, Previc in 1993 concluded that only the utricles may be responsible for the sympathetic activation. Thus, it was highly desirable to develop an animal model in which otolithic inputs are selectively removed and the sympathetic response of the cardiovascular system to orthostatic stress be measured. This proposed research project attempted to eliminate utricular sympathetic inputs by selectively destroying hair cells of the otolith organs (of the utricles in particular) in animals by exposing them to extremely high and prolonged Gy stimulation (+, - or both). Comparisons of the results from this "new" model were planned to be made against the current "gold standard" of a labyrinthectomy which consists of an invasive/ surgical ablation of the entire vestibular apparatus. The specific objective of this project was to determine the roles of the utricles in sympathetically mediated cardiovascular function. The specific measure of sympathetic function was to be changes in G-induced loss of consciousness (G-LOC) induction time and cardiac output during +Gz stress. It was felt that this information would greatly enhance the understanding of the overall physiology of G-tolerance and could aid in the development of novel countermeasures and/or vestibular screening procedures to prevent G-LOC.

Unfortunately, budget cuts resulted in a reduction in the overall requested budget of this project by 62%. As a result we were only able to attempt the model development portion of the project and the remainder of this report provides those details and preliminary results.

## METHODS:

a. Labyrinthectomy: Either unilateral labyrinthectomies or sham operations will be performed on anesthetized rats (Ketamine HCL- 35mg/kg), with paired sets of sham and control operations will be performed on the same day. The bulla is exposed on one side by blunt dissection via a skin incision near the angle of the mandible and a pediatric otic speculum placed over the bone to maintain retraction of soft tissues. The ventral surface of the bulla is removed with a fine dental burr and microrongeurs to expose the middle ear cavity. In the labyrinthectomy group, the base of the cochlea is opened with a dental burr and small picks to expose the vestibule and the otolith organs and semicircular canal cristae is ablated with a curette and aspiration. This procedure ablates the neuroepithelium, without involvement of the ossicular chain, tympanic membrane, internal acoustic canal, cochlear nerve, facial nerve, or Scarpa's ganglion. For the sham operations, the bony labyrinth is touched with either a fine burr or a small curette. The bulla is then sealed with Gelfoam and the wound closed with sutures. Anesthesia is reversed by administration of the opiate antagonist naloxone ( $0.4 \text{ mg} \cdot \text{kg body mass}^{-1}$ , IM).

b. High Gy Exposures: A rat restraint chamber (figure 1) was fabricated and mounted on the small animal centrifuge perpendicular to the arm. This restraint apparatus could be pinned to prevent it from "swinging out" during rotation of the centrifuge arm. This configuration results in a predominantly Gy exposure. A conceptual picture of this arrangement is provided (figure 2).

## RESULTS:

A systematic search was conducted for the optimal Gy magnitude and duration-dose needed to elicit utricular lesions without systemic harm to the animal. The initial G-protocol consisted of a single exposure to +70 Gy for 90 sec on day one followed by a second identical exposure on day two with the restraint device rotated  $180^\circ$  (-70 Gy). To verify the lesion process a righting reflex test was performed daily for one week followed by sacrifice of the rat. The necropsy report was negative and the vestibular apparatus histology revealed only slight damage to the utricular and saccular organs. To enhance the likelihood of successful lesions the G-dose was doubled for the next experiment (2 exposures/day to +70 Gy for 90 sec, 15 minutes apart, 2 consecutive days). As shown in figure 3, the centrifuged vestibular lesion group resulted in a gradual and linear decrease in righting reflex which plateaued at about 7 days post-exposure. Additional confirmation of vestibular lesions was obtained from histological examination of vestibular system sections. Figure 4 is an example of one such section. In this micrograph there is evidence of physical damage to the cellular trabeculae that normally connects the membranous labyrinth to the bone and a rupture of the membranous labyrinth between the utricular macula and the horizontal semicircular canal crista. These abnormalities suggests that the trabeculae which suspends the membranous labyrinth are being sheared/torn within the vestibule and the membranous labyrinth is being ruptured (or even "scrambled") by the high +/-Gy exposures. In contrast to centrifugal ablation of the vestibular system, labyrinthectomized rats demonstrated a

reverse pattern of vestibular function/righting reflex changes. On day one post-surgery righting ability was essentially zero; but improvements occurred over time. By day 19 post-lesion there was an approximately 50% recovery of righting reflex suggesting some form of compensation.

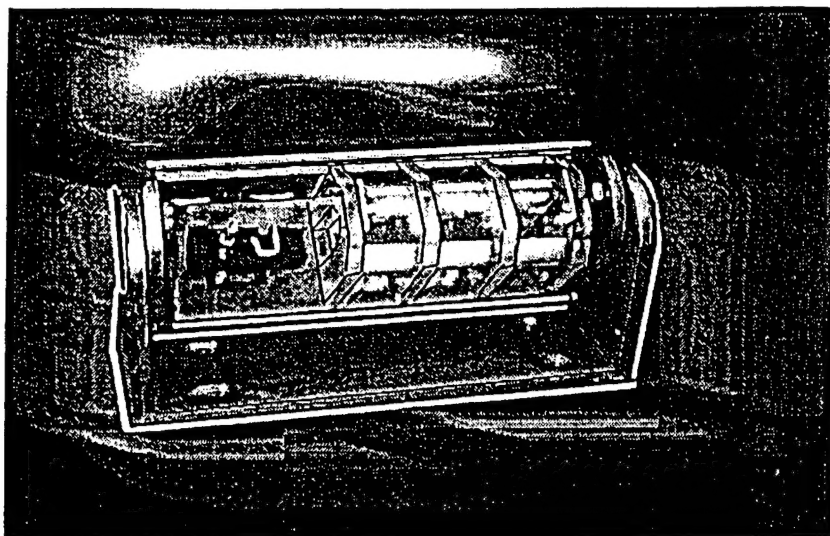
#### CONCLUSION:

Due to budget restraints it was only possible to meet one of our two objectives. We were able to develop a utricular hair cell lesion model by prolonged centrifugation of rats in the Gy axis. This method of eliminating vestibular influence offers the advantage of being fairly "non-invasive" and would be our method of choice in lieu of labyrinthectomies. We were not able to complete the main objective of this project, namely, to determine the roles of the utricles in sympathetically mediated cardiovascular function.

#### Reference:

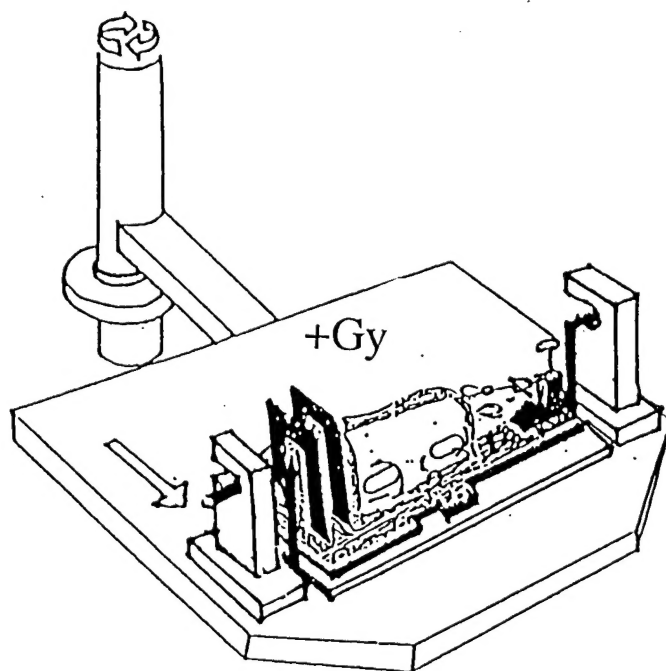
Previc, F.H. Do the organs of the labyrinth differentially influence the sympathetic and parasympathetic systems? *Neurosci. Biobehav. Rev.* 17:397-404, 1993.

FIGURE 1



Drawing of Plexiglas rat restraint chamber for high Gy exposures

FIGURE 2



Rat centrifuge arm alignment for Gy acceleration vector

FIGURE 3

EFFECTS OF SURGICAL OR CENTRIFUGAL  
LESIONS ON VESTIBULAR FUNCTION

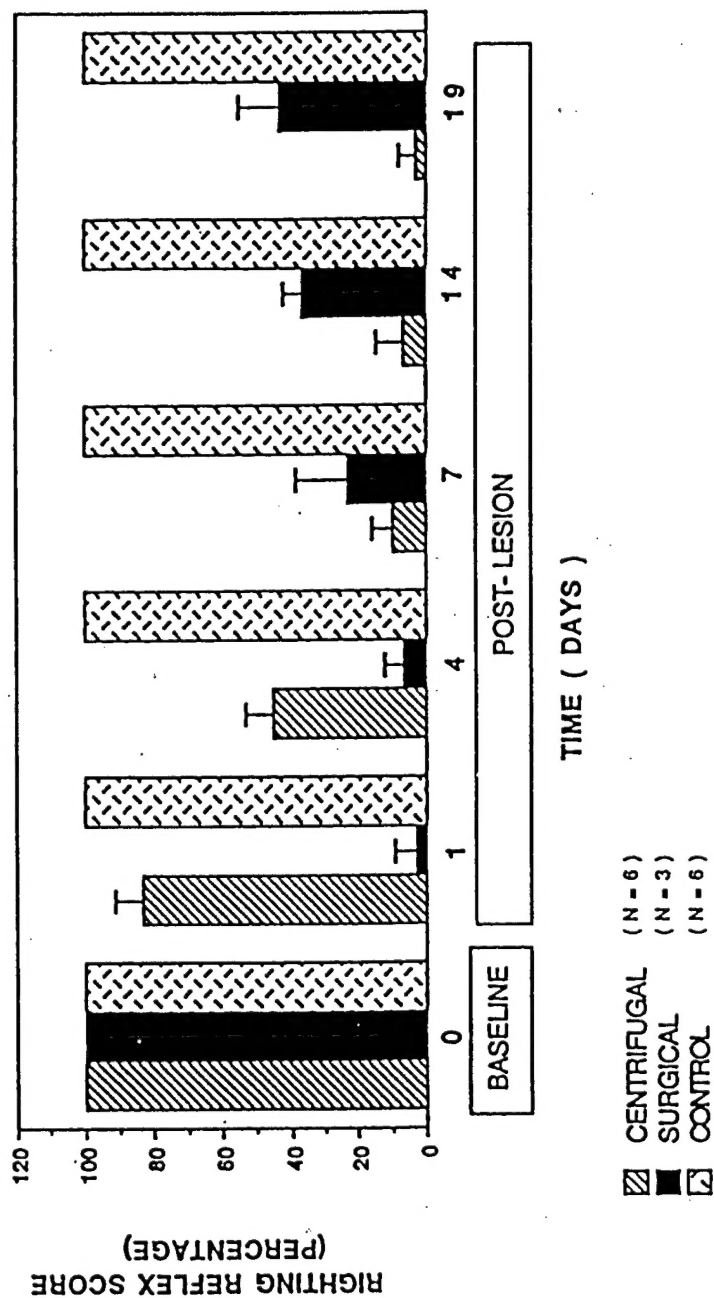
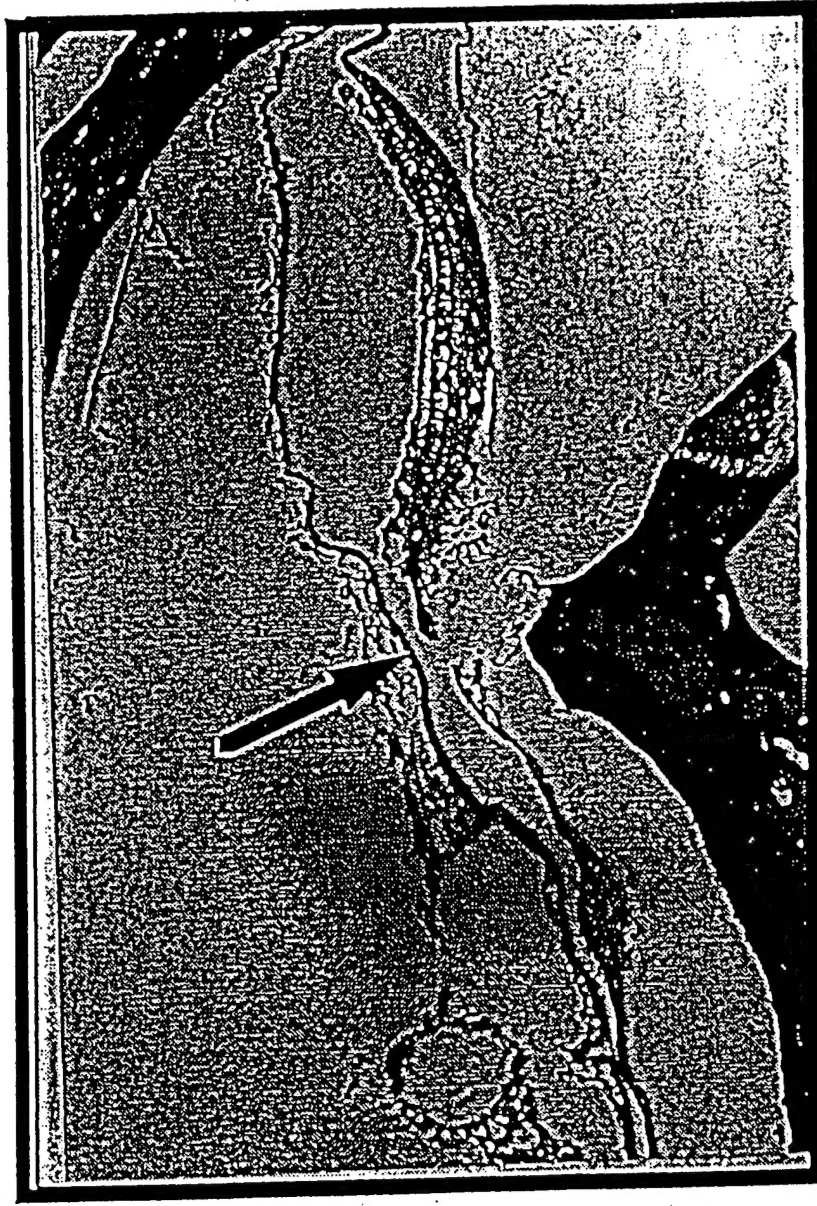


FIGURE 4



Micrograph depicting physical damage to the cellular trabeculae that normally connects the membranous labyrinth to the bone and a rupture of the membranous labyrinth between the utricular macula and the horizontal semicircular canal crista.